DRAFT

DATE: October 9, 2001

TO: Interested Parties

FROM: Stephen D. Nightingale, MD
Office of Public Health and Science

SUBJECT: Summary of September 24, 2001 Meeting - **INFORMATION**

At the request of the Secretary, a public meeting was held on September 24, 2001 from 9:05 AM to 2:25 PM to determine if and how the Department of Health and Human Services (DHHS) Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathy (BSE/TSE) Action Plan can be expanded to capitalize on the resources of the pharmaceutical and biotechnology industries. The meeting was held in the Secretary's Conference Room of the Hubert H. Humphrey Building, 200 Independence Ave. SW, Washington, DC 20201. The meeting was chaired by Dr. Arthur J. Lawrence, Acting Principal Deputy Assistant Secretary for Health, and attended by approximately 80 members of the Department and the public.

Dr. Richard Johnson of the National Institutes of Health (NIH) opened the meeting with a review of his agency's past and present BSE/TSE research portfolios. He noted that the NIH had sponsored the fundamental work on TSEs for which Carlton Gadjusek and Stanley Prusiner had received Nobel Prizes. He said that NIH currently spends about $20 million per year to fund about 70 TSE-related grants. He pointed out that most of this funding went to four laboratories: those of Dr. Prusiner, Drs. Caughey and Cheseboro, Dr. Gambetti, and Dr. Rohwer. He discussed the need for more investigators, and for more facilities in which they could work.

Dr. David Asher of the Food and Drug Administration (FDA) then discussed what is not known about human TSEs from a regulator's perspective. He observed that we do not know how many cows in how many countries are affected by BSE. He also observed that, until we know the minimum, average, and maximum incubation period for variant Creutzfeldt-Jakob disease (vCJD), we will not know how many people are affected by vCJD, either. He identified the minimum infective dose of a TSE agent; correlates of infectivity such as route of administration, species barriers, and differences among TSE agents; and the effectiveness of the various methods to reduce the spread of BSE that have been used in the United Kingdom, and that are now being

used in countries where BSE has recently been found, as areas in need of further investigation.

Dr. Asher noted that the elements of infectious risk of regulated products are the source of raw materials, the ability of the manufacturing process to reduce contamination, and the susceptibility of the end user. He mentioned the concern that there might be unknown animal reservoirs of the agents that cause various TSEs, much as cows are reservoirs of the agent that causes vCJD. He also mentioned the concern that some manufacturing processes might increase, rather than decrease, infectivity. He reminded the audience that only one genetic susceptibility, methionine homozygosity at codon 129 of the prion protein, had so far been identified for vCJD, and asked if there might be others.

Dr. Asher stated that the potential capacity of blood products or other human tissues to transmit vCJD was of particular concern to FDA, and particularly the stage of disease at which these products or tissues may become infectious. He noted that detection of abnormal prion proteins in blood and tissues, bioassays in transgenic mice, and identification of surrogate markers were all technologies in need of further development. He noted that regulators would ordinarily expect clinical validation before any candidate screening test would be considered acceptable.

Dr. Asher concluded by noting that the prion hypothesis is widely but not universally accepted. He supported further testing of this hypothesis because it is necessary for its scientific proof that this occur, because these challenges could lead to better tests for TSEs, and because they might lead to important new findings about the pathogenesis of these diseases.

Dr. Linda Detwiler of the United States Department of Agriculture (USDA) then discussed what is not known about animal TSEs from a regulator's perspective. She described two such perspectives: one on the prevention of TSEs, and the other on their detection, control, and eradication. She noted that there was precedent for eliminating animal diseases, such as bovine pleuropneumonia, without knowledge of their pathogenesis, but she identified several gaps in current knowledge that would, if corrected, facilitate prevention and control of animal TSEs.

Dr. Detwiler asked for more information about the host range of TSEs, particularly in natural settings, and for more information about individual TSE agents (particularly the agents of scrapie and chronic wasting disease), strain variations among the agent of an individual TSE, and different pathogenicities of different strains. She asked for more information about how host genotypes affect susceptibility to a TSE (or the period of its incubation), and about how host genotypes affect the distribution of infectivity in different tissues. She also asked for work on transmission of TSEs, and particularly on when asymptomatic carriers become infectious; on vertical transmission; and on the role of the environment in disease transmission. She reiterated Dr. Asher's concern that some species may serve as silent reservoirs for TSEs.

Dr. Detwiler called for better proof of the effectiveness of TSE inactivation procedures for animal tissues, for products made from them, and for the environment, and for inactivation procedures that do not harm the tissue, product, or environment being treated. She stressed the

need for diagnostic tests in live, asymptomatic animals, and the need that these tests be practical as well as sensitive, specific, and cheap.

Dr. Peter Lurie concurred with the presentations of Drs. Asher and Detwiler. He then turned to the difference between two amounts proposed for TSE research funding in FY 2003: about $300 million by Drs. Stanley Prusiner, Robert Gallo, Pieroluigi Gambetti, and Bernadine Healy, and about $30 million the Department, about $30 million by the DHHS BSE/TSE Action Plan. Dr. Lurie concurred with the view that there should be some balance between research funding and disease burden. He noted that the amount proposed by Drs. Prusiner and colleagues for a disease with about 300 incident cases per year was approximately the same amount the NIH is currently spending on diabetes, a disease with about 2.3 million incident cases per year. Dr. Lurie also expressed concern about the effectiveness of large and sudden increases for funding of particular diseases, and concern that the public might not realize a fair return on such investments.

Dr. Lurie strongly supported the endorsements of Drs. Asher and Detwiler for funding of public health research on TSEs, including human and animal surveillance, and studies of possible modes of transmission and of the effectiveness of decontamination strategies. Dr. Lurie called for more reimbursement for autopsies in suspected TSE cases, more animal testing, and better surveillance of dietary supplements.

Mr. Dennis Jackman of Aventis Behring then presented his perspective on unmet needs in BSE/TSE research, and the role of collaboration between government and industry in meeting these needs. The first need that he addressed was for a definitive study of whether blood or plasma from individuals with preclinical or clinical vCJD could transmit this disease. He noted that industry might have resources to contribute to this necessarily large study, for example transgenic mice. The second need was for a highly sensitive test for infectious prions in biological samples. He noted that industry characteristically focuses most of its own resources on the technology that appears to have the greatest likelihood of success, but might entertain opportunities for secondary participation in higher-risk ventures. The third need he addressed was to validate existing processes that remove prions from biological samples, food, and cosmetics, and the fourth was to develop better methods to achieve these goals.

Mr. Jackman indicated that his corporation was engaged in these ventures, and that it would be happy to explore government collaboration. He suggested that rights to any technology developed during a collaboration and antitrust would be issues industry would carefully explore.

Mr. Jackman noted that the European Commission has announced that it will provide up to 25 million euros per year for collaborative research with European industries on BSE/TSEs, and that Japan appears to be moving in this direction as well. He suggested that a similar initiative by the United States government initiative to promote BSE/TSE research that balanced public interest and private incentive would be favorably received by industry.

Mr. Christopher Healey of the Plasma Protein Therapeutics Association (PPTA) began by supporting Mr. Jackman's statement. Mr. Healey described the four elements of his industry's response to the threat of BSE/TSE threat: formation of expert working groups on science and public policy, enhanced communication with consumers, ongoing dialogues with regulators with the particular goal of enhancing global harmonization of regulation, and research by individual companies. He acknowledged that his industry did not feel it could solve the BSE/TSE challenge alone, and so for that reason welcomed federal support of ongoing research and support to establish new facilities where this research could be performed.

Dr. Robert Rohwer of the University of Maryland then spoke on behalf of establishing a contract laboratory where BSE/TSE research could be performed. He began by noting that although the United States has established active surveillance programs, feed bans, blood donor deferral policies, it remains vulnerable to TSEs because we do not fully understand how some of these, particularly scrapie and chronic wasting disease, are transmitted. He noted that up to 100,000 cows in the United Kingdom had been infected before the first case of BSE was recognized, and he expressed concern that there might be many more asymptomatic individuals with vCJD than currently appreciated.

Dr. Rohwer stated that progress in BSE/TSE research was slow because the TSEs progress slowly in experimental animals as well as in humans. He compared BSE/TSE research to polio research, and noted that BSE/TSE research is an order of magnitude slower and an order of magnitude more expensive. He said that for this reason it is necessary to do experiments, and collaborations, in parallel rather than serially to achieve the scientific progress we require.

Dr. Rohwer acknowledged the shortage of investigators in his field, but noted that the number was increasing, notably in Europe, and that there were more investigators who wished to collaborate with him than he had laboratory space to accommodate. This had led him to develop, three years ago, a proposal for an independent core laboratory that would serve the needs of many BSE/TSE investigators much as a large telescope serves the needs of many astronomers.

Dr. Rohwer proposed that this facility could serve needs of both academic and industry investigators, and would provide a venue where they could interact. It would broaden access to BSE/TSE research, and it would create the space necessary for large-scale titration experiments necessary to determine thresholds of infectivity. The facility might also serve the needs of regulators, and perhaps others who have need of reliable but "unglamorous" data. By concentrating research in a single facility with dedicated technical personnel, his proposal would limit the dissemination of prions, and it would establish a standard of reliability for the research community. He estimated the cost of building this facility at $350/sq ft, or about $14 million for a 40,000 sq ft facility that would house about 25,000 rodents and have about 10,000 sq ft of Biologic Safety Level 3 laboratory space.

Dr. Rohwer then addressed the need for greater availability of transgenic mice, defined antibodies, and human specimens to BSE/TSE researchers. He acknowledged the legitimate

interest of those who have developed these materials in their subsequent use, and he requested NIH purchase these materials and develop a repository for them. He anticipated an ongoing shortage of human specimens, and called for efforts to develop and validate replacements for them. Dr. Rohwer concluded by calling for longer funding cycles for those in BSE/TSE research because of the longer duration of experiments in this field.

Dr. Niel Constantine of the University of Maryland then spoke on behalf of a proposal to develop a collaboration among academic centers of clinical pathology to develop a screening test for prions in asymptomatic individuals. He stated that NIH funding for diagnostics development was limited. He proposed that funding diagnostics research should be complementary to funding a core laboratory or other basic BSE/TSE research. Dr. Constantine suggested that the consortium he proposed would be ideally suited to address the problem of minimizing false-positive tests. He said they would also have the best access to clinical specimens, and the most expertise with current diagnostic technologies.

Dr. Giles Shih of BioResources International spoke in favor of Dr. Rohwer's core laboratory proposal. His own company exploits a proprietary enzyme technology in animal feed, prion inactivation, and decontamination of medical instruments. He has done work with a European laboratory because a suitable collaborator in the United States was not available. Dr. Shih indicated he had received support from USDA to develop ways to remove prion contaminants from animal feed. He indicated he would be interested in further collaborations with either government or industry.

At this point the Secretary of Health and Human Services, Mr. Tommy G. Thompson, entered the room and addressed the meeting. The Secretary began his remarks by complimenting Dr. Lawrence for his and his staff's work since the events of September 11, and thanking those present for their contributions to this meeting. He then noted that, while current United States health policies on BSE and TSEs are based on the best scientific information currently available, more information was needed.

The Secretary recalled that earlier this year he had received a proposal from Dr. Prusiner and colleagues regarding BSE/TSE research, and that he had then directed Dr. Lawrence to lead the Public Health Service (PHS) in the development of a BSE/TSE action plan. The Secretary outlined the PHS plan, with emphasis on its NIH-directed research component. He noted that the one substantive difference between the Prusiner and the PHS plans was the amount that the government should, or perhaps in his own words could, devote to BSE/TSE research in the near future.

The Secretary said that he had requested the Acting Director of the NIH to provide additional funding from the Director's discretionary fund for this research if the proposals the NIH receives were to justify additional funding. The Secretary said that the $30 million proposed for BSE/TSE research in the FY 2003 budget - roughly double the current amount - reflected a scientific rather than a budgetary restraint. He said the actual amount could be more; however, he said if an

insufficient number of proposals pass scientific review, it could also be less.

The Secretary reiterated that today's meeting was being held to determine if the pharmaceutical and biotechnology industries wish to join academic and government researchers in pursuing NIH-sponsored research. He asked those in attendance to consider the following two questions:

> Do we now know enough to fairly and rapidly review any regulatory document you may anticipate sending us that deals with TSEs?
>
> If not, are you interested in working with us to develop that aspect of scientific knowledge about TSEs that you anticipate both of us will need.

The Secretary indicated that if the answer to the first question was no, then he hoped the answer to the second question would be yes.

In response to a question from Dr. Constantine, the Secretary indicated that new research funds could be available in FY 2002. In response to a question from Dr. Drohan, the Secretary indicated that he would consider suggestions to modify traditional grants programs to meet the specific needs of BSE/TSE investigators.

After lunch, Dr. Bruce Phelps of Chiron described his company's efforts to develop a sensitive test using accessible tissues to detect the molecular form of the prion protein that causes a TSE. He noted that Chiron had established collaborations with Dr. Fred Cohen of the University of California on the structure of prion proteins and Drs Dennis Burton and Anthony Williamson of the Scripps Research Institute on antibodies to these proteins to promote Chiron's own research capabilities. Dr. Phelps strongly supported the concept of collaboration between government and industry to accelerate development of a diagnostic test, and he encouraged the department to expand significantly the funding in the BSE/TSE Action Plan for research in this area.

Dr. William Drohan of Clearant described his company's efforts to adapt gamma radiation to the task of inactivating and removing prions from biologicals. He indicated that current efforts using 50 kr and proprietary protective agents have resulted in a one to two log reduction in prion activity without harm to the human albumin in which the prion is suspended. He stated that this technology also inactivates a broad spectrum of pathogens.

Dr. Drohan said that his company now has in the queue about 32 experiments it would like to do to confirm some of its studies, and that these experiments in its own facilities cost about half a million dollars each and would take four to five years to complete. For this reason, he strongly supported Dr. Rohwer's proposal for a core laboratory, and for government support that would accelerate the development of his company's technology.

Dr. Martin Munzer of CyGene described his company's efforts to isolate prions from biologicals

using magnetic bead-based extraction techniques and subsequent membrane-assisted, complement-mediated signal amplification equivalent to approximately 40,000 signals per target in order to achieve the level of sensitivity necessary to detect prions at biologic concentrations. Dr. Munzer anticipated his company's development of generic assays that do not require specific monoclonal antibodies to the barren prion protein, and the elimination of other steps that are used in current assays. He welcomed inquires regarding collaboration.

Dr. Neil Raven of the Center for Applied Microbiology and Research (CAMR) in Salisbury, United Kingdom, spoke on behalf of his own organization and of Genencor, Inc. CAMR is a special agency of the United Kingdom Department of Health which exists to promote collaboration between government and academic researchers for the purpose of developing practical products that will reach the marketplace. Dr. Raven stated that CAMR had secured the equivalent of $3 million for basic research on prions from the European Community, the United Kingdom Ministry of Agriculture, and the Department of Health. This funding has enabled CAMR to establish a core laboratory and develop its own core set of reagents, including over 800 parallel aliquots of fully titered BSE infectivity.

Dr. Raven said that CAMR had partnered its experience in TSE containment, validation, experimental facilities, and track record in biotherapeutics with Genencor's targeting and molecule delivery technologies to explore the best targets for prion detection efforts.

Dr. Daniel Achord on Ortho Clinical Diagnostics described his company's collaborative efforts with Caprion Pharmaceuticals to develop a blood test for vCJD, and with IDEXX Laboratories to develop tests for BSE. Dr. Achord indicated that Ortho Clinical Diagnostics was seeking partnerships with the NIH, CDC, and FDAalong with other interested parties or government agencies, to facilitate acquisition of relevant patient and primate samples and animal models for the development of an assay to detect vCJD in the blood supply.

Dr. Abraham Grossman of Q-RNA described his company's RNA-based technology to detect prion proteins. These proprietary nucleic acids, called Amplibodies, contain both a recognition and an amplification domain, and can be modified to enhance affinity or specificity for a particular target. Dr. Grossman noted that his research has been supported by the Department of Defense and by NIH, and that his interactions with these agencies had been very constructive. Dr. Grossman requested further support of research on nucleic acid diagnostics.

Dr. Peter Burke from Steris described his company's efforts to improve on existing technologies to decontaminate products exposed to pathologic prion proteins. He said that Steris is currently evaluating its proprietary decontamination technology in collaboration with United States and European researchers, and would welcome opportunities to collaborate with federal agencies. He noted that Steris would appreciate assistance in obtaining access to and funding for bioassays.

Dr. Jerry Squires of the American Red Cross then provided his organization's perspective on the amount of government support that should be provided for BSE/TSE research. He reiterated the

estimate of Dr. Prusiner and colleagues that this support should be in the range of $300 million as an initial investment over the first one or two years. Dr. Squires observed that little is known about the multiplication of pathologic prion proteins, and that little is known about how their abnormal shape contributes to their pathologic properties or their resistance to degradation. He urged that talented scientists from other research areas be recruited toTSE research, and he emphasized the amount of infrastructure that would have to be developed for this recruitment to be successful. Dr. Squires briefly summarized the major points in Dr. Prusiner's proposal for a National Prion Program, and urged its adoption.

In the discussion period that followed, Dr. Celso Bianco of America's Blood Centers spoke in support of Dr. Rohwer's proposal for a core laboratory.

Dr. Cohen suggested that efforts be made to shorten the time line for NIH research funding for BSE/TSE research. Dr. Johnson commented that funding from the Director's discretionary fund could be disbursed relatively quickly, but those disbursements had been generally for supplemental funding and infrastructure development. He reiterated that, in his view, the biggest impediment to increasing funding was the dearth of qualified investigators, and the time it would take to develop these investigators.

Dr. Drohan commented that, from his perspective in industry, he sees a different bottleneck. He said he has a number of qualified investigators at his company who have designed experiments his company is ready to fund, but there are not a sufficient number of transgenic animals available to perform these experiments. For this reason, he reiterated his support of Dr. Rohwer's proposal.

Dr. Rohwer then commented that Europe was producing an increasing number of new investigators. He said this was because the European Community has made funds available for BSE/TSE research over the past decade, and it is now paying off. Dr. Johnson agreed.

Mr. James Hayward of Q-RNA commented that, in the current economic climate, capital for investment was much more accessible to large than to start-up biotechnology companies, and the government should investigate how it might assist start-up companies obtain sufficient funding.

Mr. Jackman commented that while the prion investigators in his company were primarily focused on research of high priority to the company, there was enough flexibility in their workplace for them to apply for government funding, add some staff, and engage in some collaborative work in addition to their primary job responsibility.

Dr. Lynch commented on the question asked by the Secretary whether there was now sufficient knowledge for the government to review any regulatory document submitted to it. Dr. Lynch's answer was no. Dr. Lynch asked whether, given the very low apparent frequency of TSEs in the population to be tested for these diseases, current regulatory practices for licensing a screening test are appropriate. He then asked whether treating a wide range of source materials to reduce

the risk that end products incorporating them would transmit TSEs would require that these end products be relicensed. Dr. Lynch suggested that studies to answer these questions were not within the traditional bounds of NIH-sponsored research, and that other funding would be necessary.

Dr. Roger Dodd of the American Red Cross made the final comment, which was that some effort should be devoted to assessing the psychological and sociological impact of implementing a screening test for vCJD in blood donor or other populations.

The meeting was then adjourned.